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54 **ANTIMICROBIAL SURGICAL IMPLANTS.**

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Description

The present invention relates to endoprosthetic implants for the human or animal body and provides a manner of rendering such implants antimicrobial. The invention has particular, but not exclusive, application to orthopaedic implants.

As used in this Specification, the term "endoprosthetic implant" includes the entire implant, parts thereof and fixing means therefor. In particular, said term includes, for example, orthopaedic pins, plates and screws, and artificial joints.

With few exceptions, it has been the established practice for many years to manufacture endoprosthetic implants from materials which induce minimal tissue response and effects and yet possess adequate mechanical properties for the particular application. In the particular case of endoprosthetic orthopaedic implants structural materials usually have been sought which do not corrode *in vivo* and which do not cause bone reabsorption.

Materials used for orthopaedic implants have progressed from the early use of common metals and their alloys, especially mild steel, through the use of surgical stainless steel to the present day use of cobalt chromium molybdenum alloys and titanium and titanium alloys. Other materials which are used in endoprosthetic orthopaedic implants include ceramic and carbon-based materials and some synthetic plastics materials such as ultra-high molecular weight polyethylene, some forms of nylon, polymethylmethacrylate and silicone elastomers. None of these materials have fulfilled entirely the aim of bioinertness (i.e. bioactivity) in all circumstances, but in general the attempt usually has been towards the use of more fully inert materials to prevent as far as possible any interaction *in vivo*. The search for materials of greater bioinertness for use in surgical implants continues without diminution.

In the early years of implant surgery, silver was employed in the manufacture of endoprosthetic implants. In particular, silver wire, silver plates and silver-plated screws were used in bone repair surgery and tracheotomy tubes were silver plated. However, the use of silver and silver plated implants had generally ceased about 1935 in the ever continuing search for greater bioinertness for implant materials. In the particular case of orthopaedic implants, silver was, and still is, generally considered to be unacceptable as an implant material, because of poor mechanical properties, connective tissue reaction and excessive subperiosteal bone growth (see, for example, Venable *et al*, Ann. Surg. 105, 917—938, 1937).

Silver was one of the first metals known to man. Silver artifacts have been found in tombs dating to 4,000 B.C. It is believed that in antiquity, silver was deliberately chosen for water receptacles to conserve the quality of drinking water. Silver needles have traditionally been used in acupuncture, which is one of the oldest forms of invasive

medical treatment. The antimicrobial properties of silver compounds have been recognized for about 100 years. The first reports of silver compounds for pharmaceutical use is that of aqueous silver nitrate for preventing eye infection in new born babies. Since then a range of silver salts, colloids and complexes have been employed to prevent and control infection. Colloidal metallic silver has been used topically for conjunctivitis, urethritis and vaginitis.

The antimicrobial activity of metallic silver has been exploited in filter elements for domestic and industrial use (see Disinfection, Sterilization, and Preservation; Editor S.S. Block, Publishers Lea and Febiger, Philadelphia, 1977). For this purpose, silver has been deposited on porous carbon or used in the form of a wire, gauze or other physical shape. It is believed that the active agent is the silver ion and that impurities must be present in the metal to expedite oxidation and solution.

The body's ability to counter infection in the immediate vicinity of an implant is reduced thereby increasing the risk of a localised infection around the implant. This risk persists beyond the immediate postoperative period and is a significant complication in implant surgery. It is usually difficult to treat such infection. Often additional surgery and sometimes removal of the implant is required in order to effectively treat the infection.

It has been proposed in UK Patent Specification No. 2053687 to initially drive a silver electrode as an anode to release silver ions to create a germicidal environment at a site of living tissue to be healed and thereafter to drive the electrode as a cathode to promote healing. Reference is made to bone grafting and to the use of a biogalvanic couple to drive the silver electrode.

UK Patent Specification No. 1582016 discloses the use of silver ions to prevent infection during use of a catheter. In particular, that specification discloses a catheter in which there is an aperture adjacent to the tip of the tubular body to allow communication between the lumen and the exterior of the body. Ion producing means, which can be in the form of silver wire or powder, are positioned around the exterior and/or interior of the body to prevent infection when the catheter is in use. It is also stated that a silver cap can be mounted on one end of the tubular body to kill or inhibit the growth of pathogenic bacteria within the bladder.

Similarly, US Patent No. 4054139 discloses the coating of catheters and other percutaneous lead devices, such as shunts, cannulae, and wires, with an oligodynamic quantity of metallic silver to provide an antibacterial effect.

U.S. Patent No. 4027393 discloses the coating of orthopaedic appliances, including inter alia bone screws, plates, nails, pins and prosthesis with silver and, after implanting the appliance, driving the silver as an anode of a constant current generator.

US Patent No. 3932627 discloses the application of a silver-heparin-allantoin complex to poly-

meric prosthetic valves, arterial grafts and the like to avoid thrombus formation and infection.

It has been proposed that inorganic silver compounds should be incorporated in bone cement to reduce the risk of postoperative infection following the insertion of an endoprosthetic orthopaedic implant. In particular, J. A. Spadaro *et al* (Clinical Orthopaedics and Related Research, 143, 266—270, 1979) proposed that low concentrations of inorganic silver compounds should be incorporated in polymethylmethacrylate bone cement for this purpose. The compounds which they evaluated for this purpose were silver chloride (AgCl), silver oxide (Ag₂O), silver sulphate (Ag₂SO₄), silver phosphate (Ag₃PO₄) and chlorided silver (Ag—AgCl). They report that their proposal was based upon the known antibacterial effects of silver ions. The least effective of the compounds evaluated was chlorided silver which at 0.5% concentration did not inhibit any of the three bacteria tested, viz *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. In contrast, each of the other compounds evaluated significantly inhibited the bacteria at 0.5% concentration except for silver chloride which did not inhibit *Escherichia coli* at that concentration.

It has also been reported by the same workers that electrically generated silver ions constitute a potent broad spectrum antibacterial agent of use as adjunctive treatment in the management of chronic osteomyelitis (Becker *et al.*, J. Bone and Joint Surg., 60A, 871—881, 1978). The silver iontophoresis was used after standard surgical treatment for osteomyelitis, including debridement and the opening of all pockets of infection. When the wound was to be surgically closed, silver wire electrodes were temporarily inserted for a period of about six weeks. Electrical current was applied to the electrode from an external power source.

It is specifically stated in Becker *et al* (*supra*) that the clinical utility of silver is limited and, in particular, that diffusion of silver ions from a metallic surface such as silver foil is negligible. This statement is consistent with the absence, to the best of our knowledge, of any reported observation of significant antimicrobial activity when using the prior art silver or silver coated implants. Further, it is consistent with our own tests which had shown that commercially available 99.99% pure silver bar and foil do not inhibit the *in vitro* growth of *Staphylococcus aureus*.

Having regard to the above, the present state of the art can be summarized as being that, despite the reported antimicrobial activity of certain forms of metallic silver and its use before about 1935 in surgical implants, the use of metallic silver in endoprosthetic implants is contraindicated. Further, recent developments in the field of orthopaedic surgery teach the use of silver salts and electrically generated silver ions but not metallic silver surfaces for the prophylactic or adjunctive treatment of postoperative infections following implant surgery.

It is the object of the present invention to

provide a simple, effective and surgically acceptable manner of rendering endoprosthetic implants antimicrobial to provide a prophylactic treatment of postoperative infection. Surprisingly, it has been found that this object can be achieved by going against the long established teachings of the art and using metallic (including alloyed) silver, provided that two criteria are met. One criteria is that the metallic silver should be activated in the sense that it erodes *in vivo* to provide a sustained release of silver ions at a concentration sufficient to produce a localized antimicrobial effect but insufficient to cause significant damage to connective tissue. The other criteria is that the structural material of the implant should be a substantially bioinert material so that the mechanical integrity of the implant is retained despite the erosion of the metallic silver.

According to one aspect of the present invention there is provided an endoprosthetic implant (as hereinbefore defined) comprising a permanent implant structure formed of a substantially bioinert structural material providing permanent mechanical integrity to the implant and a metallic silver component deposited in or on said permanent implant structure, characterised in that the silver component has been activated by (a) heating at a temperature in excess of about 180°C or (b) contact with hydrogen peroxide so that it is bioerodible to provide *in vivo* a sustained release of silver ions in a concentration sufficient to provide a localized antimicrobial effect but insufficient to cause significant damage to connective tissue.

In another aspect of the present invention, there is provided a method of rendering antimicrobial an endoprosthetic implant comprising a permanent implant structure formed of a substantially bioinert structural material providing permanent mechanical integrity to the implant and a latently bioerodible metallic silver component deposited in or on the permanent implant structure, said method comprising (a) heating at a temperature in excess of about 180°C or (b) contact with hydrogen peroxide to render said silver component bioerodible to provide *in vivo* a sustained release of silver ions in a concentration sufficient to provide localized antimicrobial effect but insufficient to cause significant damage to connective tissue.

As mentioned previously, the invention has particular, but not exclusive, application to endoprosthetic orthopaedic implants. However the invention is applicable to any endoprosthetic implant which has permanent structural integrity. The permanent implant structure can be made of any structural material which is substantially bioinert but usually will be of titanium or titanium alloy or cobalt chrome molybdenum alloy, or ceramic material, or non-toxic synthetic plastics material, or any combination of these materials. Examples of implants to which the invention has particular application include orthopaedic plates, pins and screws, and artificial joints.

The metallic silver component can be made of

commercially pure (i.e. 99.99%) silver metal or of a silver alloy, for example a dental amalgam or silver solder. In order to promote galvanic action producing silver ions, there can be used an alloy of silver with a more noble metal such as gold or platinum.

The silver will be deposited in or on the permanent implant structure. Conveniently, the silver component is constituted by surface coating on at least part of the implant structure. However, the component can be constituted in other ways, for example as a deposit in one or more cavities provided in the permanent implant structure or as a permeant in a porous substrate in or on the permanent implant structure.

The location of the silver component in the implant will be selected having regard to the structure and intended application of the implant. In the case of a silver coating, said coating can extend over all or only a selected part or parts of the implant structure. Similarly, in the case of cavity-deposited silver or permeant silver, the silver can be distributed over the implant structure or provided only at a selected part or parts thereof.

The quantity of silver in the composite implant and the rate of erosion *in vivo* is such as to provide a sustained release of silver ions in sufficient concentration to produce a localized antimicrobial effect but insufficient to produce significant damage to connective tissue. The required concentration balance readily can be achieved because antimicrobial activity is provided at a concentration of the order of nanogrammes/ml whereas connective tissue damage appears to require concentrations of six orders higher, i.e. milligrammes/ml. Nevertheless, the cumulative effects of sustained release of silver ions in the body must be considered when determining the quantity of silver to be used and the rate of erosion to avoid toxic effects in the human or animal body. Any osteogenesis produced by the antimicrobial concentrations of silver can be tolerated and in any cases actually can be advantageous in that, for example, an orthopaedic implant is more securely located and/or the bone thickened in an area of weakness where it is joined to the implant.

It has been found that the quantity of silver in the composite implant suitably is the amount corresponding to a surface coating of 10 to 1000 Angstroms applied over the entire surface of the implant. This corresponds in the case of a large implant such as an artificial hip joint to not more than about 2 mg silver with proportionally smaller amounts of silver for smaller implants. Usually, an amount corresponding to such a coating of 25 to 500 Angstroms thick will be used.

It is an essential feature of the invention that the metallic silver component should be bioerodible to provide *in vivo* the silver ions required for the desired antimicrobial activity. As previously stated, metallic silver surfaces such as silver bar, silver foil and silver coatings applied by conventional plating techniques are not significantly anti-

microbial or at least lose any antimicrobial activity shortly after manufacture. Moreover, the preoperative treatment of surgical implants at the time when silver or silver-plated implants were in use was such that the silver content of said implants would not have been suitably activated to become antimicrobial. In particular, sterilization would have been conducted using temperatures of no more than about 100°C and/or sterilizing agents, such as alcohol, which do not activate the silver content to bioerode. However, metallic silver can be rendered suitably bioerodible by the chemical or thermal treatment discussed below.

An existing metallic silver surface can be activated thermally by heating to a temperature in excess of about 180°C. The duration of heating required to activate the surface will depend upon the temperature and the nature of the surface. Usually a temperature in the range of 200°C to 270°C will be used for a period of 16 to 60 mins. It has been found surprisingly that the surface is activated either in a molecular oxygen-containing atmosphere such as gaseous oxygen or air, or in an inert atmosphere, such as gaseous argon or nitrogen.

The presently preferred manner of activating existing metallic silver surfaces is to treat the surface with hydrogen peroxide. Preferably, the implant is immersed in the hydrogen peroxide. Suitably, 10 to 100 vols hydrogen peroxide is employed for a contact time of about 20 mins. The preference for this method is based upon convenience of use especially in view of the ready availability of hydrogen peroxide in operating theatres, where it is used to irrigate wounds at the time of operation.

The present invention affords many advantages over current proposals and methods of dealing with postoperative infection following implant surgery. In particular, it provides a prophylactic treatment which at least reduces the risk of post-operative infection and which can be regularly employed in implant surgery. The composite implant is self-contained requiring no energy source, such as electrical current, to produce the antimicrobial activity. Said activity is provided merely by bioerosion of the silver component. The silver ions so released are not accompanied by irritant and toxic cations such as those generated by freely dissociable salts such as silver nitrate. Further, it is less likely that the antimicrobial activity of silver ions will be circumvented by such relatively minor genetic mutation in a micro-organism as will often circumvent the anti-microbial activity of an antibiotic.

The following is a description, by way of example only and with reference to the accompanying drawings, of embodiments of the present invention. In the drawings:—

Figure 1 is a photograph of an incubated culture plate in which is located an implant which is partly coated with silver;

Figure 2 is a photograph of an incubated culture plate in which are located implant screws;

Figures 3, 4 and 5 are photographs of incubated

culture plates in which are located implant screws which are partly coated with silver;

Figure 6 is a photograph of an incubated culture plate in which a silver bar was located during incubation but was subsequently removed;

Figure 7 is a photograph of an incubated culture plate in which is located a silver bar;

Figures 8, 9 and 10 are photographs of incubated culture plates in which are located silver foil discs.

Referring first of Figure 1, the bottom half 1 of an implant pin 2 of titanium alloy type 318 was coated with silver by film evaporation. The thus coated pin was autoclaved in a conventional modern operating theatre autoclave with steam at about 140°C followed by a hot air drying cycle. After cooling, it was then placed on a culture plate 3 which had been inoculated with *Staphylococcus aureus* and the culture incubated for 24 hours. As can be seen in Figure 1, there was a clearly apparent zone 4 of inhibition around the silver coated bottom half 1 but no inhibition around the top half of the pin 2.

Referring now to Figure 2, three screws 5 of titanium alloy type 318 which had not been subjected to any special treatment were placed on a culture plate 23 which was inoculated and incubated as described above. As can be seen in Figure 2, there was no inhibition of *Staph. aureus*.

Three titanium alloy screws identical to the screws 5 of Figure 2 were coated with a 35 nm layer of silver at their upper halves only by sputter coating. The partly coated screws 45 (see Figure 3) were heated in air for 1 hour at 250°C and then autoclaved with steam at 120°C. After cooling, the autoclaved screws 45 were placed on a culture plate 43, which was inoculated and incubated as described above. As can be seen in Figure 3, there were clearly apparent zones 44 of inhibition around the coated upper halves of the screws 45 but no inhibition around their bottom halves.

Two titanium alloy screws identical to the screws 5 of Figure 2 were sputter coated with a 35 nm layer of silver at their upper halves only and subsequently heated in air for 1 hour at 250°C. After cooling, the partly coated screws 55 (see Figure 4) were placed on a culture plate 53, which was inoculated and incubated as described above. As can be seen in Figure 4, inhibition occurred only in zones 54 around the silver coated top halves of the screws 55.

Three titanium alloy screws identical to the screws 5 of Figure 2 were sputter coated with a 35 nm layer of silver at their upper halves only, subsequently heated in air for 1 hour at 250°C and then autoclaved in a theatre autoclave at 140°C with steam followed by a hot air drying cycle. After cooling, the partly coated screws 65 (see Figure 5) were placed on a culture plate 63, which was inoculated and incubated as described above. As can be seen in Figure 5, inhibition occurred only in zones 64 around the silver coated top halves of the screws 65.

A commercially available silver bar (99.99%

purity) was heated in air at 225°C for 1 hour and, after cooling, placed on an empty culture plate. Culture medium was poured onto the plate and then inoculated with *Staph. aureus* (top half) and *E. coli* (bottom half) and incubated as described above. As can be seen in Figure 6, there was a clearly apparent zone of inhibition surrounding the location of the silver bar (subsequently removed) in the culture plate 73.

The procedure described above with reference to Figure 7 was repeated except that the culture medium and bar 86 (see Figure 7) were refrigerated for 24 hours before inoculation. As can be seen in Figure 7, there was a clearly apparent zone 84 of inhibition in the culture plate 83 around the bar 86.

Four discs of silver foil (99.99% purity) 97 (see Figure 8) were heated at 270°C for 20 mins in gaseous oxygen and, after cooling, placed on a culture plate 93, which was inoculated and incubated as described above. As can be seen in Figure 8, there were clearly apparent zones 84 of inhibition surrounding the discs 97.

The procedure described above with reference to Figure 8 was repeated except that the discs 107 (see Figure 9) were heated in gaseous nitrogen instead of oxygen. As can be seen in Figure 9, there were clearly apparent zones 104 of inhibition in the culture plate 103 surrounding the discs 101.

Three discs of silver foil (99.99% purity) 117 (see Figure 10) were immersed in 100 vol% hydrogen peroxide for 20 mins. The discs were thoroughly washed with water to remove all traces of hydrogen peroxide and then placed on a culture plate 113, which was inoculated and incubated as described above. As can be seen in Figure 10, there were clearly apparent zones 114 of inhibition around the discs 113.

Tests with the activated foil discs 97, 107 and 117 show that their antimicrobial activity is retained for at least 8 weeks when stored in air at room temperature.

Claims

1. An endoprosthetic implant comprising a permanent implant structure formed of a substantially bioinert structural material providing permanent mechanical integrity to the implant and a metallic silver component deposited in or on said permanent implant structure (2) characterised in that the silver component has been activated by (a) heating at a temperature in excess of about 180°C or (b) contact with hydrogen peroxide so that it is bioerodible to provide *in vivo* a sustained release of silver ions in a concentration sufficient to provide a localized antimicrobial effect but insufficient to cause significant damage to connective tissue.

2. An implant as claimed in Claim 1, wherein the metallic silver is a silver alloy.

3. An implant as claimed in Claim 1 or Claim 2, wherein the silver component is constituted by a

surface coating on at least part of the implant structure.

4. An implant as claimed in Claim 1 or Claim 2, wherein the silver is deposited in or on a substrate of more readily bioerodible material.

5. An implant as claimed in any one of the preceding Claims, wherein the amount of silver in the composite implant would be sufficient to provide a surface coating of 25 to 500 Angstroms thick applied over the entire surface of the implant.

6. An implant as claimed in any one of the preceding Claims, wherein said activation has been by heating at a temperature of 200° to 270°C for 16 to 60 mins.

7. An implant as claimed in any one of Claims 1 to 5, wherein said activation has been by contact with 10 to 100 vols hydrogen peroxide for about 20 mins.

8. A method of rendering antimicrobial an endoprosthetic implant comprising a permanent implant structure formed of a substantially bioinert structural material providing permanent mechanical integrity to the implant and a bioerodible metallic silver component deposited in or on the permanent implant structure, said method comprising (a) heating of a temperature in excess of about 180°C or (b) contact with hydrogen peroxide to render said silver component bioerodible such as to provide *in vivo* a sustained release of silver ions in a concentration sufficient to provide a localized antimicrobial effect but insufficient to cause significant damage to connective tissue.

9. A method as claimed in Claim 8, wherein said bioerodible metallic silver component is heated at a temperature of 200° to 270°C for 16 to 60 mins.

10. A method as claimed in Claim 8, wherein said bioerodible metallic silver component is contacted with 10 to 100 vols hydrogen peroxide for about 20 mins.

Revendications

1. Un implant prothétique interne comportant une structure d'implant permanente constituée d'une matière de structure essentiellement bioinerte assurant l'intégrité mécanique permanente de l'implant et d'un composant métallique à base d'argent déposé dans ou sur ladite structure d'implant permanente (2), caractérisé en ce que le composant à base d'argent a été activé par (a) chauffage à une température dépassant 180°C environ ou (b) contact avec du peroxyde d'hydrogène, de sorte qu'il est biodégradable pour fournir *in vivo* une source durable d'ions argent à une concentration suffisante pour fournir un effet antimicrobien localisé mais insuffisante pour provoquer des dommages notables au tissu de liaison.

2. Un implant selon la revendication 1, dans lequel le composant métallique à base d'argent est un alliage d'argent.

3. Un implant selon la revendication 1 ou la revendication 2, dans lequel le composant à base

d'argent est constitué par un revêtement de surface sur au moins une partie de la structure de l'implant.

4. Un implant selon la revendication 1 ou la revendication 2, dans lequel l'argent est déposé dans ou sur un substrat de matière plus facilement biodégradable.

5. Un implant selon l'une quelconque des revendications précédentes, dans lequel la quantité d'argent dans l'implant composite est suffisante pour constituer un revêtement de surface de 25 à 500 angströms d'épaisseur appliqué sur toute la surface de l'implant.

6. Un implant selon l'une quelconque des revendications précédentes, dans lequel ladite activation a été effectuée par chauffage à une température de 200 à 270°C pendant 16 à 60 mn.

7. Un implant selon l'une quelconque des revendications 1 à 5, dans lequel ladite activation a été effectuée par contact avec 10 à 100 volumes de peroxyde d'hydrogène pendant 20 minutes environ.

8. Un procédé pour rendre antimicrobien un implant prothétique interne comportant une structure d'implant permanente constituée d'une matière de structure essentiellement bioinerte assurant l'intégrité mécanique permanente de l'implant et d'un composant métallique à base d'argent déposé dans ou sur ladite structure d'implant permanente, ledit procédé comportant (a) un chauffage à une température dépassant 180°C environ ou (b) une mise en contact avec du peroxyde d'hydrogène pour rendre ledit composé à base d'argent biodégradable de manière à fournir *in vivo* une source durable d'ions argent à une concentration suffisante pour fournir un effet antimicrobien localisé mais insuffisante pour provoquer des dommages notables au tissu de liaison.

9. Un procédé selon la revendication 8, dans lequel ledit composant métallique à base d'argent biodégradable est chauffé à une température de 200 à 270°C pendant 16 à 60 mn.

10. Un procédé selon la revendication 8, dans lequel ledit composé métallique biodégradable est mis en contact avec 10 à 100 volumes de peroxyde d'hydrogène pendant 20 minutes environ.

Patentansprüche

1. Endoprothetisches Implantat mit einem beständigen Implantataufbau, gebildet aus einem im wesentlichen bioinerten Aufbaumaterial, welches dem Implantat eine beständige mechanische Einheit erbringt, und aus einer metallischen Silberkomponente, die in oder auf dem beständigen Implantataufbau (2) abgelagert ist, dadurch gekennzeichnet, daß die Silberkomponente aktiviert wurde durch (a) Aufheizen auf eine Temperatur, die etwa 180°C übersteigt, oder (b) durch Kontakt mit Wasserstoffperoxid, so daß sie biologisch abtragbar ist, um *in vivo* eine fortwährende Freigabe von Silberionen in einer Konzentration zu schaffen, die ausreicht, um eine

lokalisierte antimikrobielle Wirkung zu erbringen, aber die unzureichend ist, um eine bedeutende Beschädigung des Bindegewebes zu bewirken.

2. Implantat nach Anspruch 1, dadurch gekennzeichnet, daß das metallische Silber eine Silberlegierung ist.

3. Implantat nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Silberkomponente aus einer Oberflächenbeschichtung auf wenigstens einem Teil des Implantataufbaus gebildet ist.

4. Implantat nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das Silber in oder auf einem Substrat aus einem leichter biologisch abtragbaren Material abgelagert ist.

5. Implantat nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Menge des Silbers in dem zusammengesetzten Implantat ausreichend ist, um eine Oberflächenbeschichtung von 25 bis 500 Angström Stärke über die gesamte Oberfläche des Implantats zu bilden.

6. Implantat nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Aktivierung bei einer Erwärmung auf eine Temperatur von 200° bis 270°C während 16 bis 60 Minuten erfolgt.

7. Implantat nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß die Aktivierung durch Kontakt mit 10 bis 100 Volumen Wasserstoffperoxid gegenüber dem Volumen des Silbers

bei etwa 20 Minuten erfolgt.

8. Verfahren zur antimikrobiellen Schaffung eines endoprothetischen Implantates mit einem beständigen Implantataufbau, gebildet aus einem im wesentlichen bioinerten Aufbaumaterial, welches eine dauerhafte mechanische Einheit für das Implantat erbringt und aus einer biologisch abtragbaren metallischen Silberkomponente, die in oder auf dem beständigen Implantataufbau abgelagert ist, gekennzeichnet durch (a) die Erwärmung auf eine Temperatur von mehr als etwa 180°C oder (b) durch In-Kontakt-Bringen mit Wasserstoffperoxid, um die Silberkomponente biologisch abtragbar zu machen, derart, daß in vivo eine fortwährende Freigabe von Silberionen in einer Konzentration erfolgt, die ausreichend ist, um eine lokale antimikrobielle Wirkung zu erbringen, aber die unzureichend ist, um eine bedeutende Beschädigung des Bindegewebes zu bewirken.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß die biologisch abtragbare metallische Silberkomponente auf eine Temperatur von 200° bis 270°C in einem Zeitraum von 16 bis 60 Minuten erwärmt wird.

10. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß die biologisch abtragbare metallische Silberkomponente mit 10 bis 100 Volumen Wasserstoffperoxid gegenüber dem Volumen der Silberkomponente für etwa 20 Minuten in Kontakt gebracht wird.

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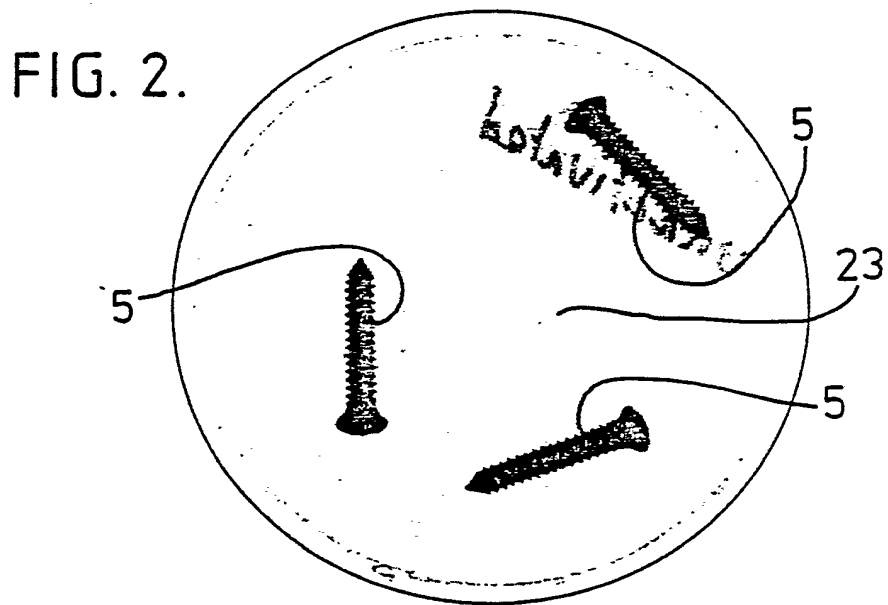
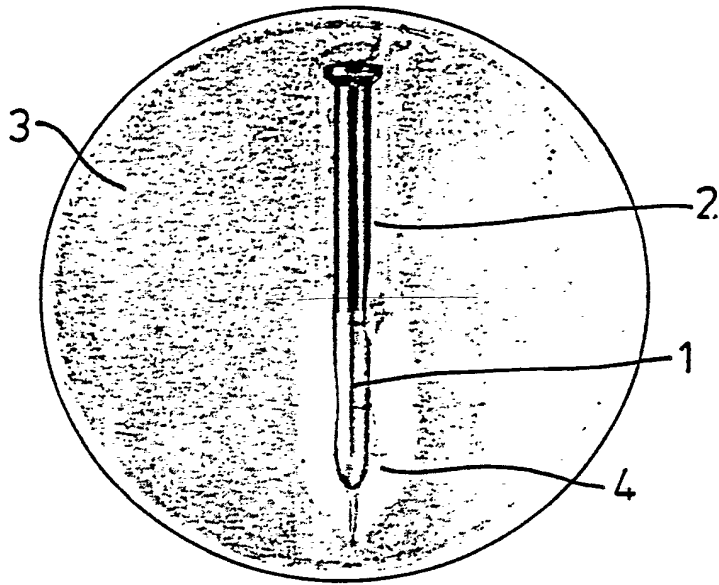
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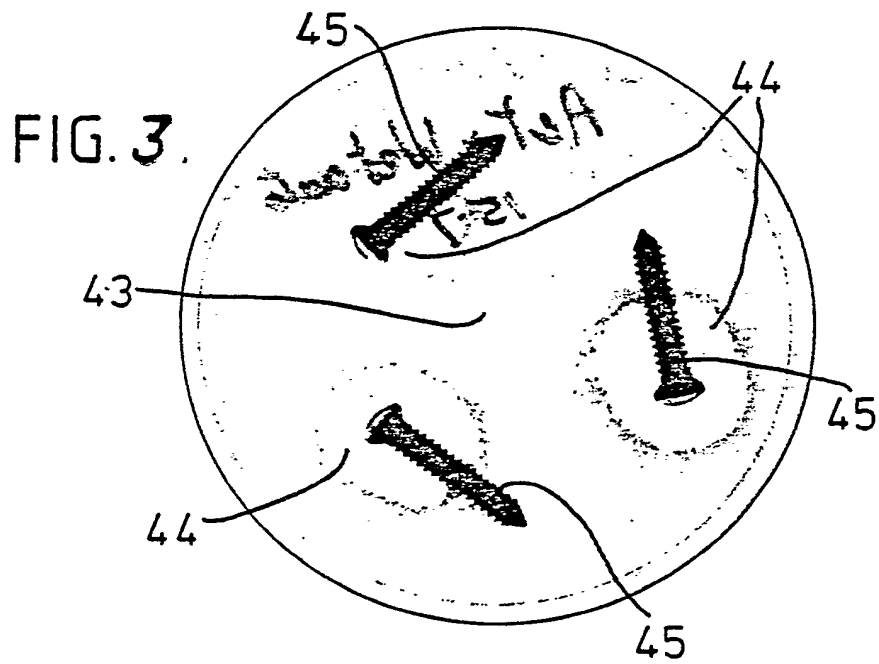
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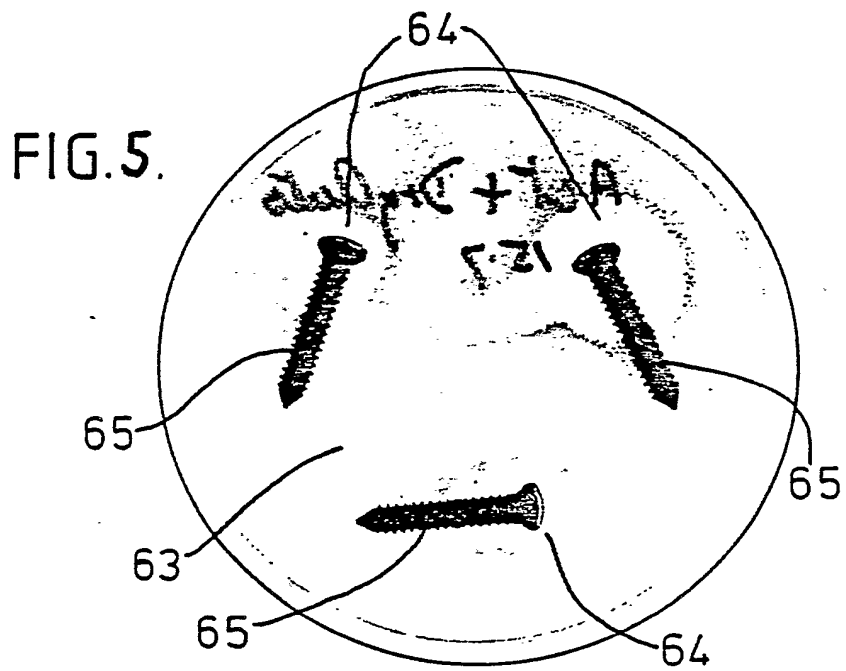
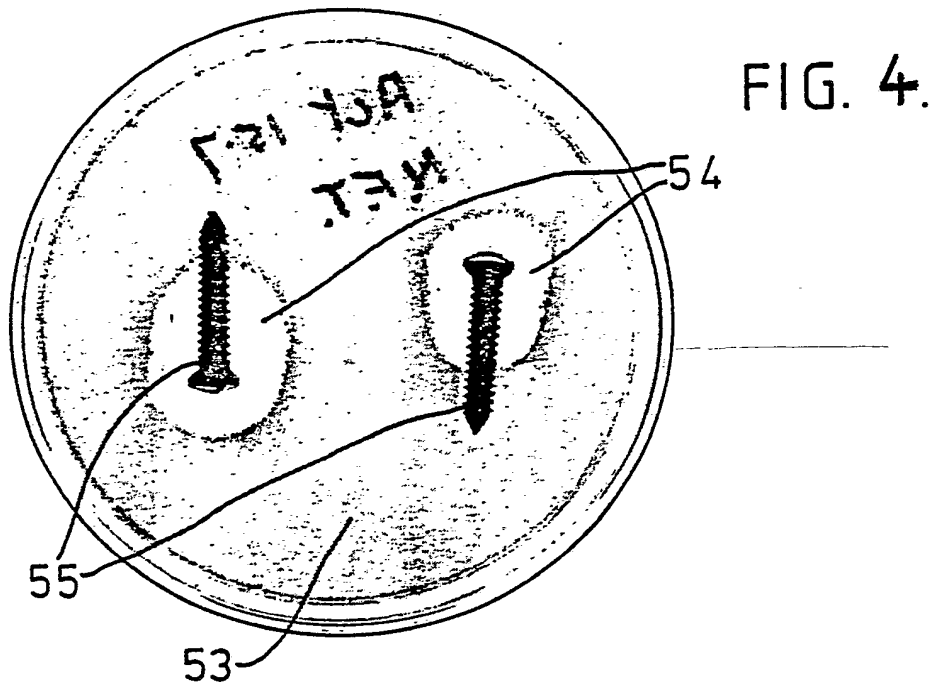
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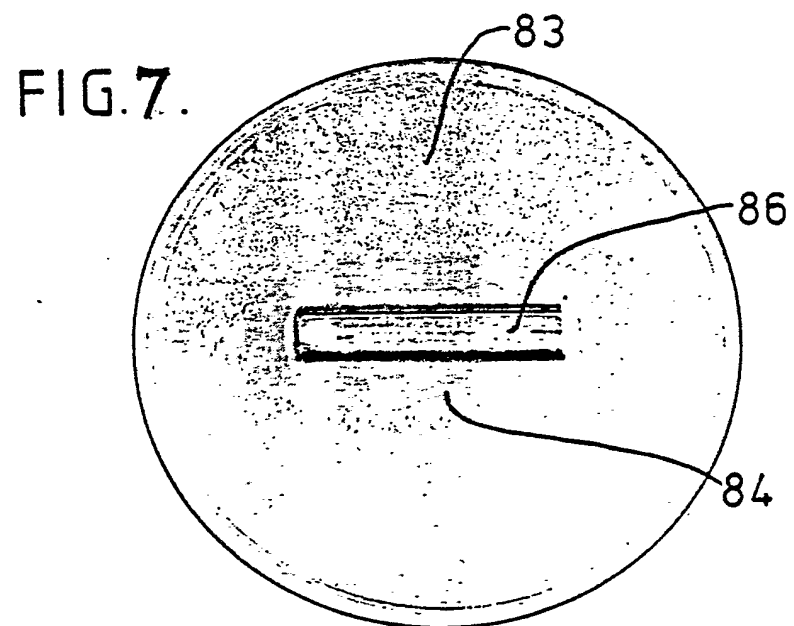
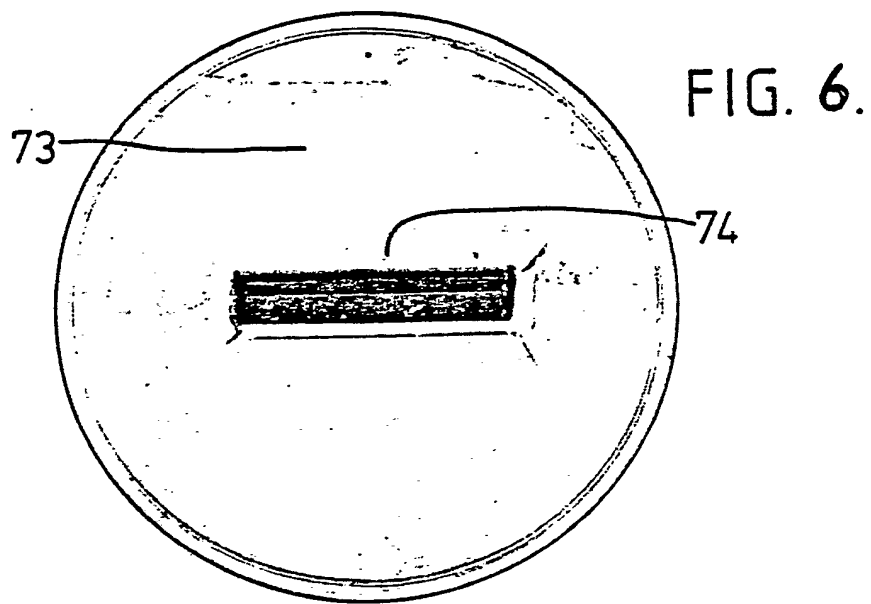
65

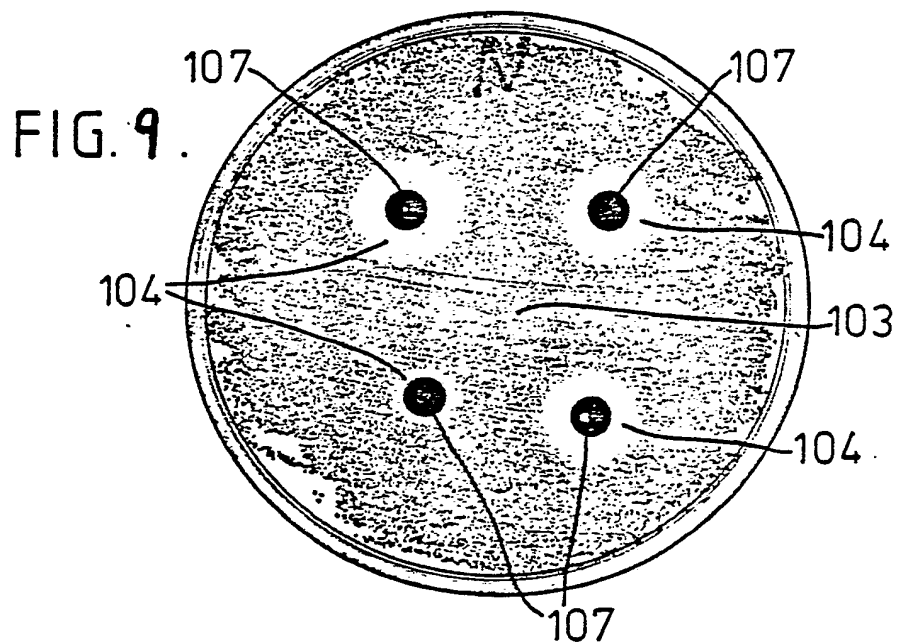
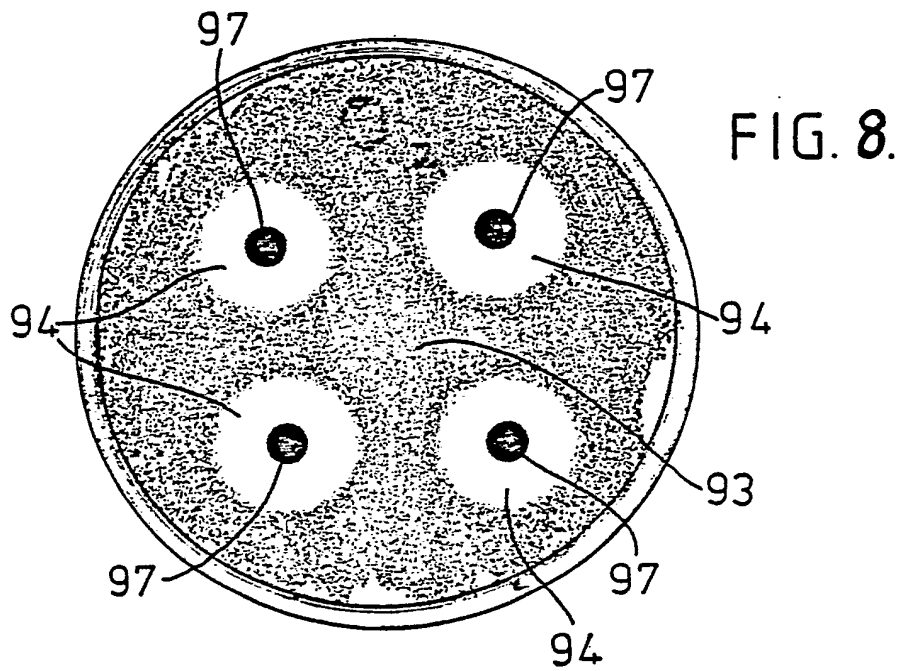
7











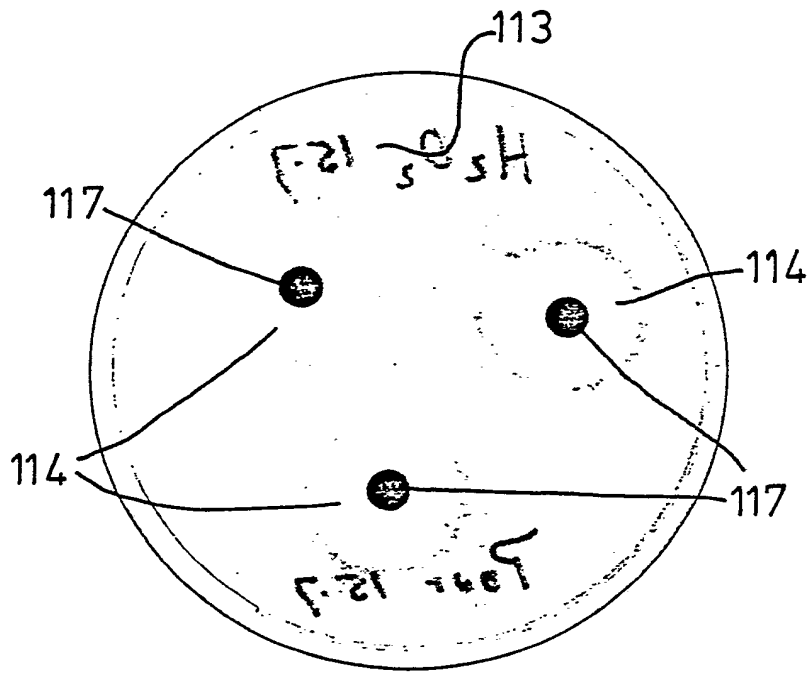


FIG. 10.